

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

40-341

APPLICATION NUMBER:

APPROVAL LETTER

JUL 26 1999

Endo Pharmaceuticals, Inc.
Attention: Carol Patterson
500 Endo Blvd.
Garden City, NY 11530

Dear Madam:

This is in reference to your abbreviated new drug application dated November 9, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Oxycodone and Acetaminophen Tablets USP, 7.5 mg/500 mg, respectively, and Oxycodone and Acetaminophen Tablets USP, 10 mg/650 mg, respectively.

Reference is also made to your amendments dated June 16, July 1, and July 20, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug products, Oxycodone and Acetaminophen Tablets USP, 7.5 mg/500 mg and Oxycodone and Acetaminophen Tablets USP, 10 mg/650 mg, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 7/26/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH
40-341**

APPLICATION NUMBER:

APPROVED DRAFT LABELING



63481-622-25

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: Dillberg Pharma
Wilmington, DE 19880

10 mg/650 mg

PERCOCET®
10 mg/650 mg
NEW STRENGTH

ENDO LABORATORIES
PERCOCET®
(Oxycodone and Acetaminophen Tablets, USP)

Multiple Strengths:
2.5/325, 5/325,
7.5/500 or
10/650 mg. Do not
dispense unless
strength is stated.
Each tablet contains:
Oxycodone Hydrochloride
10 mg and Acetaminophen
650 mg.
Usual Dosage: For dosage and full prescribing information, read accompanying product information.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
FOR HOSPITAL USE ONLY

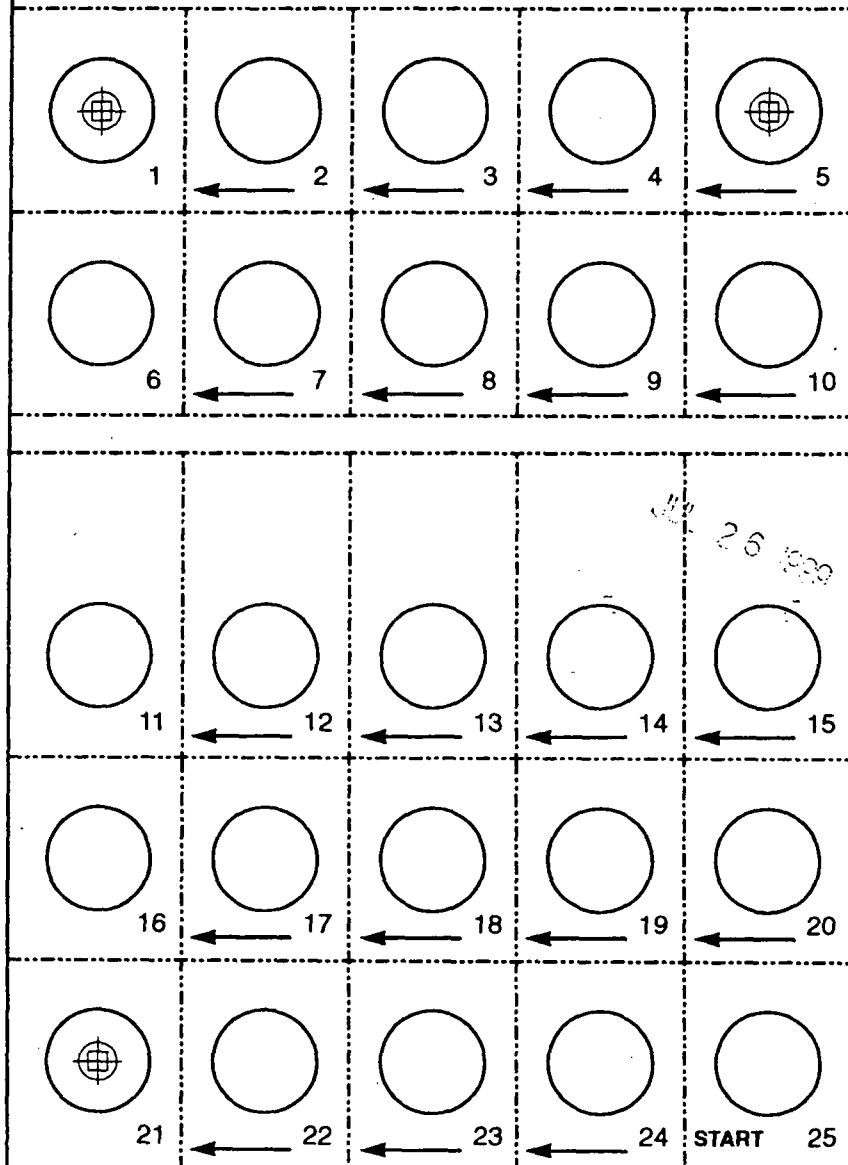
<p>PERCOCET® (Oxycodone HCl 10 mg Acetaminophen 650 mg Tablet, USP) Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP:</p> <p>BAR CODE TO BE INSERTED BY VENDOR.</p>	<p>PERCOCET® (Oxycodone HCl 10 mg Acetaminophen 650 mg Tablet, USP) Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP:</p> <p>BAR CODE TO BE INSERTED BY VENDOR.</p>	<p>PERCOCET® (Oxycodone HCl 10 mg Acetaminophen 650 mg Tablet, USP) Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP:</p> <p>BAR CODE TO BE INSERTED BY VENDOR.</p>	<p>PERCOCET® (Oxycodone HCl 10 mg Acetaminophen 650 mg Tablet, USP) Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP:</p> <p>BAR CODE TO BE INSERTED BY VENDOR.</p>	<p>PERCOCET® (Oxycodone HCl 10 mg Acetaminophen 650 mg Tablet, USP) Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP:</p> <p>BAR CODE TO BE INSERTED BY VENDOR.</p>	<p>PERCOCET® (Oxycodone HCl 10 mg Acetaminophen 650 mg Tablet, USP) Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP:</p> <p>BAR CODE TO BE INSERTED BY VENDOR.</p>
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26

BLISTER PACK - BACK

DIRECTIONS:

1. START WITH UNIT #25 (LOWER RIGHT CORNER) AND WORK SEQUENTIALLY BACKWARDS TO #1.
2. FOR BEDSIDE DISPENSING: TEAR OFF BLISTER ALONG PERFORATIONS.
3. FOR CLINIC DISPENSING: PUSH TABLET OUT BY PRESSING BLISTER.



PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.	PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.	PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.	PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.
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PERCOCET® (Oxycodone and Acetaminophen Tablets, USP) 7.5 mg/500 mg

PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.	PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.	PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.	PERCOCET® (Oxycodone HCl) 7.5 mg Acetaminophen 500 mg Tablet, USP Manufactured for: Endo Pharmaceuticals Inc. Chadds Ford, PA 19317 LOT: EXP: BAR CODE TO BE INSERTED BY VENDOR.
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Rx only

Endo

PERCOCET®
 (Oxycodone and Acetaminophen
 Tablets, USP)



**7.5 mg/500 mg
 NEW STRENGTH**

NDC 63481-621-25

Multiple Strengths:
 2.5/325, 5/325,
 7.5/500 or
 10/650 mg. Do not
 dispense unless
 strength is stated.

Each tablet contains:
 Oxycodone Hydrochloride 7.5 mg*
 Acetaminophen, USP 500 mg
 FD&C Yellow No. 6 Aluminum Lake as a color additive.
 *7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.
 Usual Dosage: For dosage and full prescribing information, read accompanying product information.
 DEA ORDER FORM REQUIRED.
 Store at controlled room temperature 15°-30°C (59°-86°F).
 25 TABLETS FOR HOSPITAL USE ONLY

45954/4594/OF

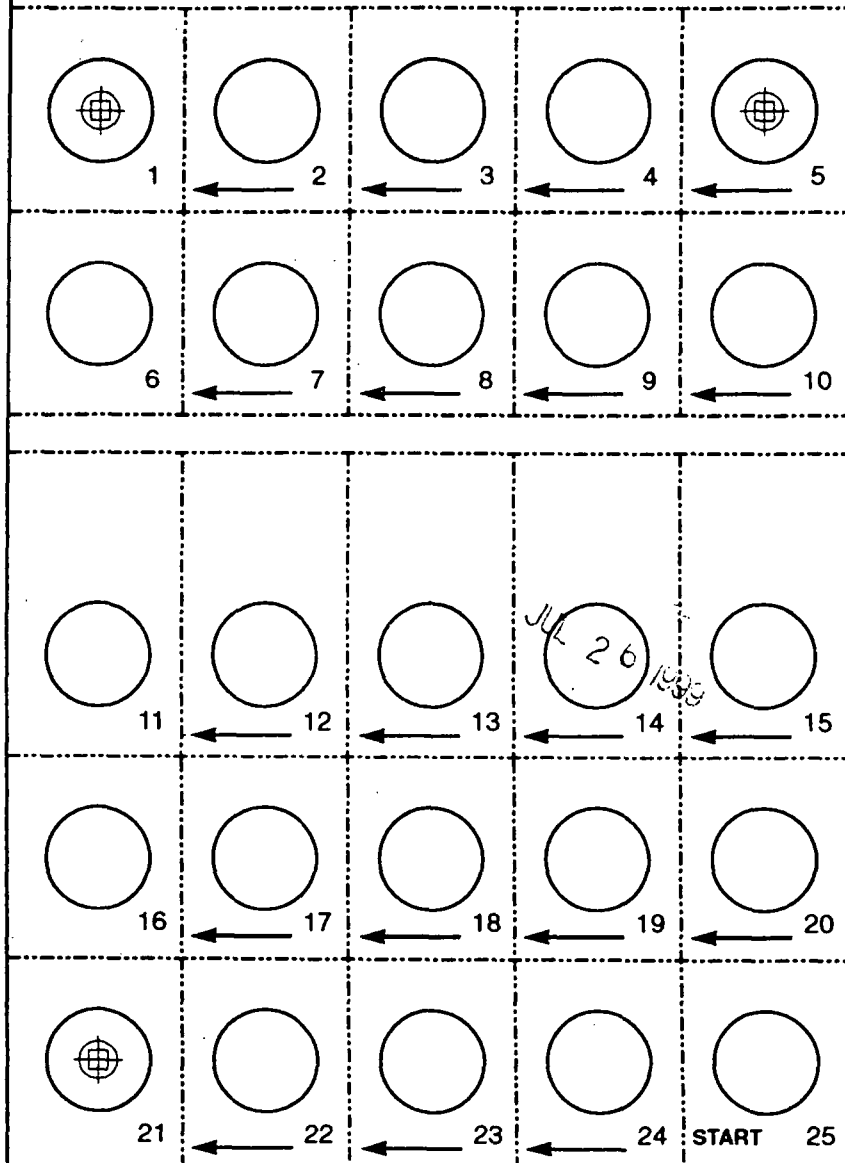
Manufactured for:
 Endo Pharmaceuticals Inc.
 Chadds Ford, PA 19317
 By: DuPont Pharmaceuticals
 Wilmington, DE 19880



BLISTER PACK - BACK

DIRECTIONS:

1. START WITH UNIT #25 (LOWER RIGHT CORNER) AND WORK SEQUENTIALLY BACKWARDS TO #1.
2. FOR BEDSIDE DISPENSING: TEAR OFF BLISTER ALONG PERFORATIONS.
3. FOR CLINIC DISPENSING: PUSH TABLET OUT BY PRESSING BLISTER.



NDC 63481-622-85

ENDO LABORATORIES

Endo

PERCOCET®

(Oxycodone and
Acetaminophen Tablets, USP)



R_x only

Each tablet contains:
Oxycodone Hydrochloride . . . 10 mg*
Acetaminophen, USP . . . 650 mg
*10 mg oxycodone HCl is equivalent
to 8.9637 mg of oxycodone.

Usual Dosage: For dosage and full
prescribing information, read
accompanying product information.
Dispense in a tight, light-resistant
container as defined in the USP.
This is a bulk package and not
intended for dispensing.

Store at controlled room temperature
15°-30°C (59°-86°F).

DEA ORDER FORM REQUIRED

500 TABLETS

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: DuPont Pharma
Wilmington, DE 19860



63481-622-85

70452/OF

ENDO LABORATORIES
PERCOCET®
(Oxycodone and Acetaminophen
Tablets, USP)

Caution

Each tablet contains:
Oxycodone Hydrochloride 10 mg
Acetaminophen, USP 650 mg
*10 mg oxycodone HCl is equivalent to 8.9637 mg
of oxycodone.

Usual Dosage: For dosage and full prescribing information, read accompanying product information.
Dispense in a light, light-resistant container as defined in the USP, with a child-resistant closure (as required).
Store at controlled room temperature 15°-30°C (59°-86°F).
DEA ORDER FORM REQUIRED

100 TABLETS

Manufactured for:
Endo Pharmaceuticals Inc.
Carrollton, PA 15117
By: Endo Pharmaceuticals
Carrollton, PA 15117

63481-622-70

NDC 63481-621-85

ENDO LABORATORIES

Endo

PERCOCET®

(Oxycodone and
Acetaminophen Tablets, USP)



Rx only

Each tablet contains:
Oxycodone Hydrochloride 7.5 mg
Acetaminophen, USP 500 mg
FD&C Yellow No. 6 Aluminum Lake as a
color additive.
*7.5 mg oxycodone HCl is equivalent to
6.7228 mg of oxycodone.

Usual Dosage: For dosage and full
prescribing information, read
accompanying product information.
Dispense in a tight, light-resistant
container as defined in the USP.

This is a bulk package and not
intended for dispensing.

Store at controlled room temperature
15°-30°C (59°-86°F).

DEA ORDER FORM REQUIRED.

500 TABLETS


Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: DuPont Pharma
Wilmington, DE 19880

7045WOF

100 TABLETS

ENDC 63481-621-70

ENDO LABORATORIES

Endo PERCOCET® 

(Oxycodone and Acetaminophen
Tablets, USP)

PERCOCET

R

Each tablet contains:
Oxycodone Hydrochloride 7.5 mg
Acetaminophen, USP 500 mg
FD&C Yellow No. 6 Aluminum Lake as a color additive.
*7.5 mg oxycodone HCl is equivalent to 6.7226 mg
of oxycodone.

Usual Dosage: For dosage and full prescribing information, read accompanying product information.
Dispense in a tight, light-resistant container as defined in the
USP, with a child-resistant closure (as required).
Store at controlled room temperature 15°-30°C
(59°-86°F).
DEA ORDER FORM REQUIRED.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317
By: DuPont Pharma
Wilmington, DE 19800

7044901

63481-621-70

Endo
ENDO LABORATORIES

PERCOCET®
(Oxycodone and Acetaminophen Tablets, USP)



R_x only

DESCRIPTION

Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:

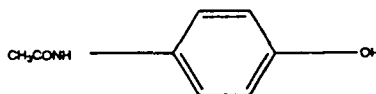
Oxycodone Hydrochloride	7.5 mg*
Acetaminophen, USP	500 mg

Oxycodone Hydrochloride	10 mg*
Acetaminophen, USP	650 mg

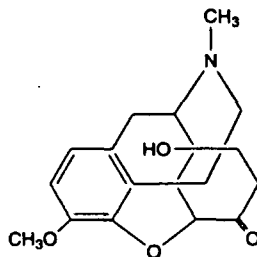
- * 7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.

Both strengths of PERCOCET also contain the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid. In addition, the 7.5 mg/500 mg strength contains FD&C Yellow No. 6 Aluminum Lake and the 10 mg/650 mg strength contains D&C Yellow No. 10 Aluminum Lake.

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.17. It may be represented by the following structural formula:



Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic pure opioid agonist which occurs as a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4 \cdot HCl$ and the molecular weight 351.83. It is derived from the opium alkaloid thebaine, and may be represented by the following structural formula:



CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent involves the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in PERCOCET are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

PERCOCET should not be administered to patients who are hypersensitive to oxycodone, acetaminophen, or any other components of this product.

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-containing medications, PERCOCET is subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of PERCOCET or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: PERCOCET should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET should be cautioned accordingly.

Drug Interactions

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with opioids may produce paralytic ileus.

Usage in Pregnancy

Teratogenic Effects; Pregnancy Category C: Animal reproductive studies have not been conducted with PERCOCET. It is also not known whether PERCOCET can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. PERCOCET should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects: Use of opioids during pregnancy may produce physical dependence in the neonate.

Labor and Delivery: As with all opioids, administration of PERCOCET to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

Nursing Mothers

It is not known whether PERCOCET is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PERCOCET is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

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An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of PERCOCET 7.5 mg/500 mg is 8 tablets and the maximal daily dose of PERCOCET 10 mg/650 mg is 6 tablets).

HOW SUPPLIED

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is supplied as follows:

7.5 mg/500 mg	Bottles of 100	NDC 63481-621-70
Peach capsule-shaped	Bottles of 500	NDC 63481-621-85
tablet embossed with	Unit dose package	NDC 63481-621-75
"PERCOCET" on one	of 100 tablets	
side and "7.5" on the other.		

10 mg/650 mg	Bottles of 100	NDC 63481-622-70
Yellow oval tablet,	Bottles of 500	NDC 63481-622-85
embossed with	Unit dose package	NDC 63481-622-75
"PERCOCET" on one side	of 100 tablets	
and "10" on the other.		

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

DEA Order Form Required.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317.



Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880

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Printed in U.S.A.

6513-00/June, 1999

4
An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is given orally. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams (maximal daily dose of PERCOCET 7.5 mg/500 mg is 8 tablets and the maximal daily dose of PERCOCET 10 mg/650 mg is 6 tablets).

HOW SUPPLIED

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is supplied as follows:

7.5 mg/500 mg	Bottles of 100	NDC 63481-621-70
Peach capsule-shaped	Bottles of 500	NDC 63481-621-85
tablet embossed with	Unit dose package	NDC 63481-621-75
"PERCOCET" on one	of 100 tablets	
side and "7.5" on the other.		

10 mg/650 mg	Bottles of 100	NDC 63481-622-70
Yellow oval tablet,	Bottles of 500	NDC 63481-622-85
embossed with	Unit dose package	NDC 63481-622-75
"PERCOCET" on one side	of 100 tablets	
and "10" on the other.		

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

DEA Order Form Required.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317



Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880

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Printed in U.S.A.

6513-00/June, 1999

NDC 63481-622-75

Endo[®] ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and Acetaminophen
Tablets, USP)



ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and
Acetaminophen
Tablets, USP)

Multiple
Strengths:
2.5/325, 5/325,
7.5/500 or
10/650 mg. Do not
dispense unless
strength is
on label.

NDC 63481-622-75

Endo[®] ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and Acetaminophen
Tablets, USP)



ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and
Acetaminophen
Tablets, USP)

Each tablet contains:
Oxycodone Hydrochloride 10 mg
Acetaminophen, USP 650 mg
10 mg oxycodone HCl is equivalent to 8.9037 mg of oxycodone.
Usual Dosage: For dosage and full prescribing information,
read accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
100 TABLETS (Four 25-tablet Blister Packs)
FOR HOSPITAL USE ONLY

R_x only

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19885

67%

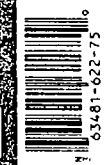
Each tablet contains:
Oxycodone Hydrochloride 10 mg
Acetaminophen, USP 650 mg
10 mg oxycodone HCl is equivalent to 8.9037 mg of oxycodone.
Usual Dosage: For dosage and full prescribing information,
read accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature 15°-30°C (59°-86°F).
100 TABLETS (Four 25-tablet Blister Packs)
FOR HOSPITAL USE ONLY

R_x only

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19885

LOT:



Multiple Strengths: 2.5/325, 5/325, 7.5/500 or 10/650 mg. Do not dispense unless strength is stated.

NDC 63481-622-75

Endo[®] ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and Acetaminophen
Tablets, USP)



ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and
Acetaminophen
Tablets, USP)

100 TABLETS

Each tablet contains:
Oxycodone Hydrochloride 10 mg
Acetaminophen, USP 650 mg
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.

R_x only

Usual Dosage: For dosage and full prescribing information, read accompanying product information.

This unit-dose package is not child-resistant.

DEA ORDER FORM REQUIRED.

Store at controlled room temperature 15°-30°C (59°-86°F).

100 TABLETS (Four 25-Tablet Blister Packs)

FOR HOSPITAL USE ONLY

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880

Each tabl
Oxycodo
Acetamin
10 mg o

Usual Do
read acc

This unit

DEA OR

Store at c

100 TAB

FOR HOS

Manufactur
Endo Pharm
Chadds For

Each tablet contains
Oxycodone Hydrochloride 10 mg
Acetaminophen, USP 650 mg
*10 mg Oxycodone HCl is equivalent to 0.8637 mg of oxycodone

Rx only

Usual Dosage: For dosage and full prescribing information,
read accompanying product information.

This unit-dose package is not child-resistant.

DEA ORDER FORM REQUIRED.

Store at controlled room temperature 15°-30°C (59°-86°F).

**100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY**

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880

Each tab
Oxycodo
Acetamin
*10 mg o

Usual Do
read acco

This unit-

DEA ORD

Store at c

100 TABL
FOR HOS

Manufactur
Endo Pharm
Chadds For

8749/OF

Each tablet contains:
Oxycodone Hydrochloride 10 mg
Acetaminophen, USP 650 mg
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.

R_x only

Usual Dosage: For dosage and full prescribing information, read accompanying product information.

This unit-dose package is not child-resistant.

DEA ORDER FORM REQUIRED

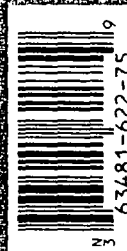
Store at controlled room temperature 15°-30°C (59°-86°F).

**100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY**

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
DuPont Pharma
Wilmington, DE 19880

LOT:
EXP:



8749/OF

Multiple
Strengths:
2.5/325, 5/325,
7.5/500 &
10/650 mg. Do not
dispense unless
strength is
stated.

NDC 63481-621-75

Endo[®] ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and Acetaminophen
Tablets, USP)



ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and
Acetaminophen
Tablets, USP)

NDC 63481-621-75

Endo[®] ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and Acetaminophen
Tablets, USP)



ENDO LABORATORIES
PERCOCET[®]
(Oxycodone and
Acetaminophen
Tablets, USP)

Each tablet contains:
Oxycodone Hydrochloride 7.5 mg
Acetaminophen, USP 600 mg
FDAC Yellow No. 6 Aluminum Lake as a color additive.
7.5 mg Oxycodone HCl is equivalent to 5.7228 mg of Oxycodone.
Usual Dosage: For dosage and full prescribing information,
read accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature (15°-30°C (59°-86°F)).
100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY

R_x only

Manufactured for
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by
DuPont Pharma
Wilmington, DE 19880

67%

Each tablet contains:
Oxycodone Hydrochloride 7.5 mg
Acetaminophen, USP 600 mg
FDAC Yellow No. 6 Aluminum Lake as a color additive.
7.5 mg Oxycodone HCl is equivalent to 5.7228 mg of Oxycodone.
Usual Dosage: For dosage and full prescribing information,
read accompanying product information.
This unit-dose package is not child-resistant.
DEA ORDER FORM REQUIRED.
Store at controlled room temperature (15°-30°C (59°-86°F)).
100 TABLETS (Four 25-Tablet Blister Packs)
FOR HOSPITAL USE ONLY

R_x only

Manufactured for
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by
DuPont Pharma
Wilmington, DE 19880

LOT

EXP:



**CENTER FOR DRUG EVALUATION AND
RESEARCH
40-341**

APPLICATION NUMBER:

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2 2. ANDA # 40-341

3. NAME AND ADDRESS OF APPLICANT

Endo Pharmaceuticals Inc.
500 Endo Blvd.
Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION

Innovator Product: Percocet
Innovator Company: Endo Pharmaceuticals Inc.
Patent Expiration Date: There are no patents or exclusivity
for Percocet 5 mg/325 mg Tablets manufactured by

Suitability Petition Docket Number 98P-0105/CP1 was approved
for a change in strength in both active ingredients,
November 6, 1998.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

Oxycodone and Acetaminophen Tablets, USP

7. NONPROPRIETARY NAME

Oxycodone and Acetaminophen Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
Firm	
11/09/98	Original
6/16/99	Amendment - Response to facsimile dated 6/3/99
FDA	
12/11/98	Receipt Acknowledged
6/3/99	Not Approvable Facsimile

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC

Analgesic Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder	LOA
------------	----------	------------	-----

✓ 50

151

13. DOSAGE FORM

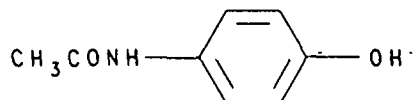
Tablet for oral administration

14. POTENCY

Strength	Strength units
7.5/500	Mg
10/650	Mg

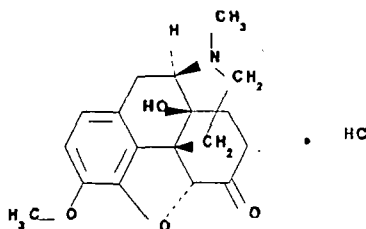
15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP
 $C_8H_9NO_2$; M.W. = 151.17



4'-Hydroxyacetanilide. CAS [103-90-2]

Oxycodone Hydrochloride USP
 $C_{18}H_{21}NO_4 \cdot HCl$; M.W. = 351.83



4,5 -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one
hydrochloride. CAS [124-90-3]

16. RECORDS AND REPORTS

1/5/99 - Bioequivalence Waiver, K. Dhariwal.
1/25/99 - Labeling Review, C. Park.

17. COMMENTS

The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory.

Waiver request granted by the Division of Bioequivalence.

Acceptable EIR issued by the Office of Compliance.

Methods Validation not required since drug substances and drug product are compendial.

The DMF's for the drug substances were satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application.

19. REVIEWER:

Glen Jon Smith

DATE COMPLETED:

July 2, 1999

Page(s) 16

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Chen Rev 2

7/2/99

1. CHEMISTRY REVIEW NO. 1 2 ANDA # 40-341

3. NAME AND ADDRESS OF APPLICANT

Endo Pharmaceuticals Inc.

500 Endo Blvd.

Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION

Innovator Product: Percocet

Innovator Company: Endo Pharmaceuticals Inc.

Patent Expiration Date: There are no patents or exclusivity for Percocet 5 mg/325 mg Tablets manufactured by

Suitability Petition Docket Number 98P-0105/CP1 was approved for a change in strength in both active ingredients, November 6, 1998.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

Oxycodone and Acetaminophen Tablets, USP

7. NONPROPRIETARY NAME

Oxycodone and Acetaminophen Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
Firm	
11/09/98	Original
FDA	
12/11/98	Receipt Acknowledged

12. RELATED IND/NDA/DMF(s)

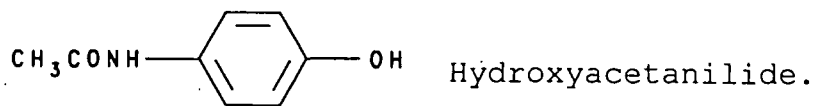
[illegible]

14. POTENCY

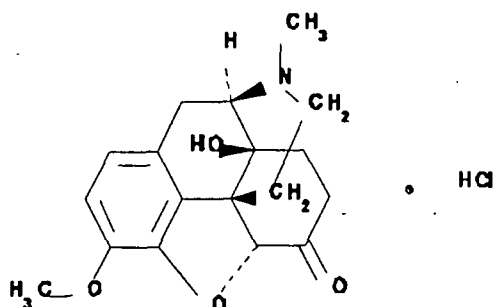
Strength	Strength units
7.5/500	Mg
10/650	Mg

15. CHEMICAL NAME AND STRUCTURE

4'-
CAS [103-90-2]



Oxycodone Hydrochloride USP
 $C_{18}H_{21}NO_4 \cdot HCl$; M.W. = 351.83



4,5 -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one
hydrochloride. CAS [124-90-3]

16. RECORDS AND REPORTS

1/5/99 - Bioequivalence Waiver, K. Dhariwal.
1/25/99 - Labeling Review, C. Park.

17. COMMENTS

Deficiencies were noted for Components and Composition,
Laboratory Controls and Stability.

Labeling was found to be unsatisfactory.

Waiver request granted by the Division of Bioequivalence.

Acceptable EIR issued by the Office of Compliance.

Methods Validation not required since drug substances and
drug product are compendial.

The DMF's for the drug substances were satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application should be considered Not Approvable -
Facsimile Amendment.

19. REVIEWER:

Glen Jon Smith

DATE COMPLETED:

April 23, 1999

Page(s) 15

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chen Row 1

4/23/99

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

40-341

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

Telephone Conversation Memorandum

ANDA: 40-341

DRUG: Oxycodone and Acetaminophen, 7.5 mg/500 mg and
10 mg/650 mg

FIRM: Endo Pharmaceuticals

PERSONS INVOLVED: Carol Patterson, Endo
Tim Ames, FDA

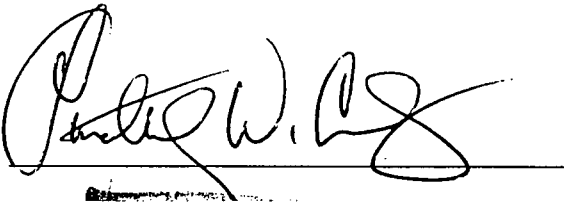
PHONE NUMBER: 516-522-3305

DATE: July 20, 1999

Firm called to request possible withdrawal of the contract testing facility, -----, as this facility is in need of an inspection and was just recently added to the EER.

Asked firm if one of the already approved testing labs could be utilized to do the testing that ----- was slated to do. It was explained to Carol Patterson that the approval of this ANDA could be delayed by weeks if ----- could not be replaced due to the necessary inspection. CPatterson agreed to pursue the withdrawal of ----- and shifting the testing responsibility to another facility.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Team 8, OGD

A handwritten signature in black ink, appearing to read 'Timothy W. Ames', is written over a horizontal line.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 40341/000**
Stamp: **09-NOV-1998** Regulatory Due:
Applicant: **ENDO PHARMS**
500 ENDO BLVD
GARDEN CITY, NY 11530

Priority: _____ Org Code: 600
Action Goal: _____ District Goal: 09-OCT-1999
Brand Name: _____
Established Name: **OXYCODONE; ACETAMINOPHEN**
Generic Name: _____
Dosage Form: **TAB (TABLET)**
Strength: **7.5/500 MG 10/650 MG**

FDA Contacts: T. AMES (HFD-640)
U. VENKATARAM (HFD-647)

301-827-5849 , Project Manager
301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 08-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No:

ICA AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment: 2437838
ENDO PHARMACEUTICALS INC
500 ENDO BLVD
GARDEN CITY, NY 11530

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: **FINISHED DOSAGE RELEASE**
TESTER

Establishment:

Jo:
A No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 14-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:

DMF No:

C AADA No:

Profile: CSN

OAI Status: NONE

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-DEC-1998

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: 11

DMF No:

Y CHEI AADA No:

Profile: CSN

OAI Status: NONE

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-MAR-1999

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment:

DMF No:

AADA No:

Profile: TCM

OAI Status: NONE

Responsibilities: FINISHED DOSAGE PACKAGER

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-DEC-1998

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

ANDA APPROVAL SUMMARY

ANDA: 40-341

DRUG PRODUCT: Oxycodone Hydrochloride
and Acetaminophen Tablets USP

FIRM: Endo
500 Endo Boulevard
Garden City, NY 11530

DOSAGE FORM: Tablet STRENGTH: 7.5 mg/500 mg
10.0 mg/650 mg

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 232) in original submission. Paragraph 306(k) certification submitted (p. 892)

EIR acceptable for drug product manufacturer and drug substance manufacturer, 3/8/99.

Facilities included:

Alternate testing laboratory for release and stability testing of the finished product.

Endo Pharmaceuticals Inc.
500 Endo Blvd.
Garden City, NY 11530

The finished product will be manufactured, packaged (bottles), labeled and tested (release and stability, all packages) by third party contract laboratories.

Manufacturing, testing, packaging (bottles), and stability testing:

I

pany
Pharmaceutical Company)

Packaging (Blister packaging), and labeling:

Drug Substance Manufacturers:

Acetaminophen USP (as Acetaminophen 90% Granulation -
Compap® L):

.....g)

Oxycodone Hydrochloride USP

Inc.
ond Street

BIO STUDY:

A change in strength for active ingredients approved per petition
by the Office of Generic Drugs, 11/6/98.

A waiver of *in vivo* bioequivalence study was granted by the
Division of Bioequivalence, K. Dhariwal, 1/5/99.

Dissolution testing results were found to be acceptable and the
firm's product was deemed bioequivalent to the reference product,
Percocet® Tablets, 5.0 mg/325 mg manufactured by Endo
Pharmaceuticals, by the Division of Bioequivalence, K. Dhariwal,
1/5/99.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

All drug substances and drug product compendial.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN
CONTAINER SECTION?:

Stability for the following included:

<u>Lot #</u>	<u>Batch Size</u>	<u>Sample</u>	<u>Test Conditions</u>
NC190		100's	40°C/75% RH/3 months
		500's	25°C/60% RH/12 months
		Blister	
NC192		100's	40°C/75% RH/3 months
		500's	25°C/60% RH/12 months
		Blister	

Container/Closure system:

100's in 150 cc, opaque white bottle, 38/400 CRC cap,
75M innerseal/liner.

500's in 950 cc, opaque white bottle, 53/400
cap, 5M innerseal/liner.

Blister Packaging in blister with foil backing, 25
blisters/sheet, 100 blisters per box.

All container/closure systems are as described in the
Container/Closure section.

Expiration date: 24 months based on accelerated stability data.

LABELING:

Description in package insert satisfactory for molecular
structure, molecular formula, formula weight, inactive
ingredients, product description and package size.

Professional labeling satisfactory per C. Park, 7/7/99.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Biowaiver batches: Lot #NC190, tablets, stability data
included. Lot #NC192, stability data included.

DMF Acetaminophen USP (as Acetaminophen 90%
satisfactory, S. Basaran, 1/27/99, no
amendments since then.

DMF Oxycodone Hydrochloride USP, it,
satisfactory, G.J.Smith, 2/26/99, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY
MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS
BIO/STABILITY?:

Executed batch records for the 7.5 mg/500 mg tablet
batch and the 10.0 mg/650 mg tablet batch
(biowaiver/stability batches) included. Blank batch records were
submitted in the application for kilogram granulation and
compression for 7.5 mg/500 mg tablets and
kilogram granulation and compression for 10.0 mg/650 mg
tablets. All scale-ups consistent with current Office policy.
Proposed manufacturing processes are the same as the
bio/stability batches.

CHEMIST:



DATE: 2/14/99

SUPERVISOR:

U.V. Vandenham

DATE: 7/14/99

CC:

251

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-341 Date of Submission: June 30, 1999

Applicant's Name: Endo Pharmaceuticals, Inc.

Established Name: Oxycodone and Acetaminophen Tablets USP,
7.5 mg/500 mg and 10 mg/650 mg

Proprietary name: Percocet®

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes (I have checked the blue jacket vol 3.1)

CONTAINER LABELS:

Satisfactory in FPL as of June 30, 1999 submission

UNIT DOSE BLISTER CARD LABEL:

Satisfactory in FPL as of June 30, 1999 submission

UNIT DOSE CARTON LABEL:

Satisfactory in FPL as of June 30, 1999 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of June 30, 1999 submission

AUXILIARY LABELING (Potency Sticker):

Satisfactory in FPL as of June 30, 1999 submission

REVISIONS NEEDED POST-APPROVAL - INSERT:

DESCRIPTION - Last paragraph, first sentence:

... a semisynthetic opioid agonist... [delete "pure"]

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes (citizen's Suitability Petition)

What is the RLD on the 356(h) form: - Percocet® (Oxycodone and Acetaminophen HCL, 5 mg/325 mg, Endo); Approved April 30, 92). This is ANDA 85-106/S-106.

ANDA Number: 85-106/S-106

ANDA Drug Name: Percocet®

ANDA Firm: Endo Pharmaceuticals Inc.

Date of Approval of ANDA Insert and supplement #:
April 30, 1992/S-106

Has this been verified by the MIS system for the ANDA?
Yes

Was this approval based upon an OGD labeling guidance No

Basis of Approval for the Container Labels: RLD

Basis of Approval for the Carton Labeling: RLD

Other Comments:

See FTR regarding the potency sticker program for the multiple strengths of this product.

FOR THE RECORD

1. MODEL LABELING - Percocet® (Oxycodone and Acetaminophen HCL, 5 mg/325 mg, Endo); Approved April 30, 92). This is ANDA 85-106/S-106.

As a reference, the followings are the dates on which other Oxycodone/Acetaminophen containing RLD products' insert labeling last approved.

88-790/S-008 Tylox® Capsules (5 mg/500 mg, Johnson) -
5/30/91

89-775/S-004 Roxicet® Tablets (5 mg/500 mg, Roxane) -
5/7/92

2. These two new strengths were found suitable for ANDA

application through the Agency's approval of the firm's Suitability Petition on November 6, 1998.

3. In agreement with the DLPS of OGD (Bob West, Charlie Hoppes, & Adolph Vezza), the firm has proposed a "potency sticker" program and submitted the sticker as suggested by the OGD to bring the health practitioner's attention to the multiple strengths of this product. Please refer to the cover letter of the firm dated June 30, 1999 and the t-con prepared by Adolph Vezza on 6/4/99 in the file folder for detail. We find the firm's proposed sticker acceptable.
4. It is noted that the firm preprinted the sticker statement on the blister card in lieu of placing a sticker. Chan Park called the firm and talked to Carol Patterson regarding this on July 7, 1999. She told that in the telecon OGD has indicated either preprint or sticker would be acceptable without any preference one to the other as long as the statement appears prominent. She has also mentioned that another two strengths, which is the subject of ANDA 40-330 has been approved for the same proposal of this potency sticker.
5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 21, 22 & 168 (Volume B.1.1).
6. The firm has replaced the term "narcotics" with "opioids" throughout the text and it should be acceptable.
7. The firm has committed that the firm's various strengths will be differentiated by using different print colors.
8. PATENTS/EXCLUSIVITIES

No issue
9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).
10. DISPENSING STATEMENT

RLD & ANDA - Dispense in a tight, light-resistant container as defined in the USP.

USP - Preserve in tight, light-resistant containers.
11. USP labeling requirement

The tablets may be labeled to indicate the content of oxycodone hydrochloride equivalent. Each mg of oxycodone is equivalent to 1.116 mg of oxycodone hydrochloride.

12. PACKAGING CONFIGURATIONS

RLD: 100s, 500s, and unit-dose 100s.

ANDA: Same as RLD

13. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.3, P.648.

14. SCORING

The RLD, Percocet® (Oxycodone and Acetaminophen, 5 mg/325 mg) by this firm is bisected whereas these two new strengths (filed by Citizen's Petition) are not scored.

15. Container/CLOSURE

Container: Plastic

Closure: CRC (SafeGard) for 100s & 500s

See comment to the chemist.

16. The firm has included a statement to read "The total daily dose of acetaminophen should not exceed 4 grams." as a last sentence under D&A section. Although this does not appear in the insert labeling of RLD yet, we should allow the firm to retain this statement. Refer to the e-mail between dr. Scheinbaum and Chan Park on this issue. Also refer to the comment under DOSAGE AND ADMINISTRATION in the last review. Currently, we are awaiting for the approval of this labeling change of NDA reference listed drug Percodan (Endo, 07-337).

(Question)

Endo Laboratories has filed an ANDA for higher strengths of Percocet (Oxycodone and APAP, 7.5 mg/500 mg & 10 mg/650 mg), whose filing was accepted through citizen's petition. The firm has proposed the proprietary name, Percocet, which is identical with the original percocet tablet (5 mg/325 mg).

We believe that this may lead to medication errors particularly if the strength is not specified in a physician's order for Percocet®. I am inclined to suggest that the firm may consider employing a similar numbering system used for "Tylenol with Codeine" to differentiate various strengths of percocet products. I would like to hear your opinion in this matter. Thank you for your help.

(Answer)

I believe it is important to state the maximum number of pills allowed. Not every doctor will remember the amount of APAP in each pill. Few will bother to look much at the label. Some may have difficulty calculating what 4 g implies and make errors. The easiest thing to remember or look

up is the maximum number of pills per day for each strength.

(This concern was addressed to the firm and the firm included this information in the insert labeling as requested.)

17. We have asked the firm to delete the second paragraph "The use of MAO inhibitors... or oxycodone." appearing in the PRECAUTIONS, Drug Interactions. This statement has been marked off from RLD insert labeling without explanation. Another generic labeling for this product (ANDA 87-406, Barr), approved January 24, 1994 (This is after the last approval of RLD insert labeling), DOES NOT CONTAIN this statement.
18. is the headquarters address for the Pharmaceutical. Per CFR 201.1(j) the sponsor opted to use the "principal place of business" in lieu of the "actual place where the product is manufactured". This explains the discrepancy between the place of business appearing in the H.S. section and "Description of Manufacturing Facility" statement.

Date of Review: 7/6/99

Date of Submission: 6/30/99

Primary Reviewer: Chan Park

Date: 7/7/99

Team Leader:

A. Vazir for C. Hoppes

Date: 7/7/99

cc:

Comments: John Hume 7/7/99

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-341

Date of Submission: November 9, 1998

Applicant's Name: Endo Pharmaceuticals, Inc.

Established Name: Oxycodone and Acetaminophen Tablets USP,
7.5 mg/500 mg and 10 mg/650 mg

Proprietary name: Percocet®

Labeling Deficiencies:

1. GENERAL COMMENTS:

We note that the proprietary name, Percocet® you have proposed for these two strengths is identical with the name of your reference listed drug. Your proposed proprietary name "Percocet®" will be forwarded to the CDER Labeling and Nomenclature Committee for review and comment. We believe that this may lead to medication errors particularly if the strength is not specified in an physician's order for Percocet®. You may consider employing a similar numbering system used for "Tylenol with Codeine" to differentiate various strengths of your products. However, we defer final comment on your proposed proprietary name pending notification of the committee's findings.

2. CONTAINER - 100s & 500s

- a. Please note that the presence of FD&C Yellow No.6 needs to be declared in the labeling, but not on the labels for the prescription drug per 21 CFR 201.20(c). You may delete this statement from the labels if you elect to do so.
- b. Revise to read "Usual Dosage" rather than "dosage".

3. UNIT DOSE BLISTER

Satisfactory in draft

4. BLISTER CARD

See comment under CONTAINER.

5. BLISTER PACK CARTON

a. See comment under CONTAINER.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, include a statement if dispensed to outpatients, it should be with a child resistant container, for example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentence is optional.]

6. INSERT

a. DESCRIPTION

i. Include the pharmacological or therapeutic class for oxycodone hydrochloride. We refer you to 21 CFR 201.57(a)(v).

ii. Revise the third paragraph (Acetaminophen occurs...) as follows:

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a ... taste. It may be represented by the following structural formula [include the structural formula of acetaminophen here].

iii. Include the molecular weight and molecular formula of both acetaminophen and oxycodone. In addition, include the structural formula for acetaminophen. Refer to 21 CFR 201.57(a)(vi) for guidance.

b. CONTRAINDICATIONS

...other components of this... [plural]

c. PRECAUTIONS

i. Drug Interactions

Delete the second paragraph.

ii. Usage in Pregnancy

A) Revise the sub-subsection heading "Pregnancy Category C" to read "Teratogenic Effects; Pregnancy Category C".

B) Nonteratogenic Effects

Use of opioids during... [rather than "narcotics" to be consistent]

d. DOSAGE AND ADMINISTRATION

With respect to the last sentence in this section, include the number of tablets for each strength in parenthesis, which correspond to the maximum allowed daily dose of acetaminophen.

e. HOW SUPPLIED

i. Please delete the statement "NARCAN® is a ...". We refer you to the GENERAL COMMENT under INSERT.

ii. We encourage the inclusion "dispense in..." statement as found on your container labels.

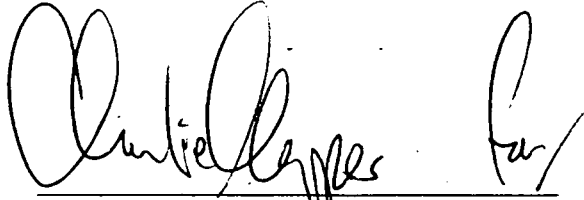
iii. The name and place of the manufacturer appearing in this section is not identical with the one described in your "Description of Manufacturing Facility" statement. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit in draft. We will not request final print pending the findings of the Labeling and Nomenclature committee regarding your proposed proprietary name.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further

review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Robert L. West", is written over a horizontal line. To the right of the signature is a large, stylized flourish or mark.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FDA CENTER
**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: **ANDA 40341/000**
Stamp: **09-NOV-1998** Regulatory Due:
Applicant: **ENDO PHARMS**
500 ENDO BLVD
GARDEN CITY, NY 11530

Priority:
Action Goal: District Goal: **09-OCT-1999**
Brand Name:
Established Name: **OXYCODONE; ACETAMINOPHEN**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **7.5/500 MG 10/650 MG**

FDA Contacts: **T. AMES (HFD-617)**
U. VENKATARAM (HFD-647)

301-827-5849 , Project Manager
301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 08-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No:

AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment: **2437838**
ENDO PHARMACEUTICALS INC
500 ENDO BLVD
GARDEN CITY, NY 11530

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE RELEASE
TESTER**

Establishment:

DMF N

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 2 of 2

Establishment:

DMF No:

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 14-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE PACKAGER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 40341/000**
Stamp: **09-NOV-1998** Regulatory Due:
Applicant: **ENDO PHARMS**
500 ENDO BLVD
GARDEN CITY, NY 11530

Priority: _____ Org Code: 600
Action Goal: _____ District Goal: 09-OCT-1999
Brand Name: _____
Established Name: OXYCODONE; ACETAMINOPHEN
Generic Name: _____
Dosage Form: TAB (TABLET)
Strength: 7.5/500 MG 10/650 MG

FDA Contacts: T. AMES (HFD-617)
U. VENKATARAM (HFD-647)

301-827-5849 , Project Manager
301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 08-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

7 No:
DA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 2437838
ENDO PHARMACEUTICALS INC
500 ENDO BLVD
GARDEN CITY, NY 11530

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**Responsibilities: FINISHED DOSAGE RELEASE
TESTER**

Establishment:

DMF N
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 14-DEC-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: 1

DMF N

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment:

DMF N

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment:

DMF No:

AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Acetaminophen and Oxycodone Tablets
500 mg/7.5 mg and 650 mg/10 mg
ANDA #40-341
Reviewer: Kuldeep R. Dhariwal
File name: 40341DW.N98

Endo Pharmaceuticals
500 Endo Blvd.
Garden City
New York 11530
Submission Date:
November 9, 1998

Review of Waiver Requests
(Electronic Submission)

The firm has submitted comparative dissolution data for acetaminophen/oxycodone tablets, 500 mg/7.5 mg and 650 mg/10 mg and is requesting for waivers of in vivo biostudy requirements. The reference listed drug is Endo's Percocet® 325 mg/5 mg tablets.

The new strengths of acetaminophen/oxycodone tablets proposed in this ANDA (500 mg/7.5 mg and 650 mg/10 mg) were found suitable for submission as an ANDA via firm's approved suitability petition (document # 98P-0105/CP1).

Formulation: Table 1

Dissolution Data: Table 2

Comments:

1. The test products are rated AA in the Orange Book and do not present bioequivalence problems.
2. The firm has used USP dissolution method. The test products meet USP specifications.
3. This ANDA is a paper and electronic submission. The electronic submission was used for review. The data in electronic submission matched well with those in hard copy.
4. The waivers can be granted.

Recommendations:

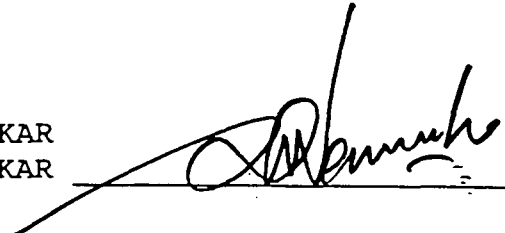
1. The Division of Bioequivalence agrees that the information submitted by Endo Pharmaceuticals demonstrates that acetaminophen/oxycodone tablets, 500 mg/7.5 mg and 650 mg/10 mg fall under 21 CFR 320.22 (c) of the Bioavailability/Bioequivalence regulations. The waivers of *in vivo* bioequivalence study requirements are granted.
2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 N HCl using USP 23 apparatus II (paddles) at 50 rpm. The test products should meet the following specifications:

Not less than _____ of the labeled amount of oxycodone and acetaminophen are dissolved in 45 minutes.

Moharwal, 1/5/99

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR



Date 1/6/1999

Concur:

Dale P. Conner
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Date 1/11/99

Table 1

Composition of Acetaminophen/Oxycodone Tablets

Ingredient	500/7.5 mg tablet (mg)	650/10 mg tablet (mg)
Oxycodone Hydrochloride, Acetaminophen*, Microcrystalline cellulose	7.50	10.00
Color D&C Yellow#6, Color D&C Yellow#10, Croscarmellose Sodium, Colloidal Silicon Dioxide,		
Stearic Acid		
Total	670.0	670.0

stearic acid

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen/Oxycodone
 Dose Strength: 500 mg/7.5 mg and 650 mg/10 mg
 ANDA No.: 40-341
 Firm: Endo Pharmaceuticals
 Submission Date: November 9, 1998
 File Name: 40341DW.N98

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
 No. Units Tested: 12
 Medium: 0.1N HCl Volume: 900 mL
 Specifications: NLT in 45 minutes
 Reference Drug: Percocet® 325 mg/5 mg (Endo)
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Reference Product Oxycodone; Lot #EMD226A Strength(mg) 5			Reference Product Acetaminophen; Lot #EMD226A Strength(mg) 325		
	Mean %	Range	%CV	Mean %	Range	%CV
15	92.3		4.9	64.2		3.9
30	98.7		2.1	78.3		9.9
45	99.7		1.4	82.7		9.9
60	100.6		1.2	84.9		9.1

Sampling Times (Minutes)	Test Product Oxycodone; Lot # NC190 Strength(mg) 7.5			Test Product Acetaminophen; Lot # NC190 Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	97.6		2.9	96.9		3.2
30	97.7		1.3	98.1		1.6
45	97.8		1.3	98.8		1.4
60	97.3		1.3	98.9		1.2

Continued...Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen/Oxycodone
 Dose Strength: 500 mg/7.5 mg and 650 mg/10 mg
 ANDA No.: 40-341
 Firm: Endo
 Submission Date: November 9, 1998
 File Name: 40341DW.N98

I. Conditions for Dissolution Testing: USP method

USP XXIII Basket: Paddle: x RPM: 50
 No. Units Tested: 12
 Medium: 0.1N HCl Volume: 900 mL
 Specifications: NLT in 45 minutes
 Reference Drug: Percocet® 325 mg/5 mg (Endo)
 Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Oxycodone; Lot # NC192 Strength(mg) 10			Test Product Acetaminophen; Lot # NC192 Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
15	98.4		4.4	97.7		3.4
30	98.9		1.6	98.5		1.6
45	98.5		1.3	98.9		1.3
60	97.9		1.3	98.9		1.1

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 40341/000	Action Goal:
Stamp: 09-NOV-1998	District Goal: 09-OCT-1999
Regulatory Due:	Brand Name:
Applicant: ENDO PHARMS	Estab. Name: OXYCODONE; ACETAMINOPHEN
500 ENDO BLVD	Generic Name:
GARDEN CITY, NY 11530	
Priority:	Dosage Form: (TABLET)
Org Code: 600	Strength: 7.5/500 MG 10/650 MG
Application Comment:	
FDA Contacts: T. AMES (HFD-617)	301-827-5849 , Project Manager
U. VENKATARAM (HFD-647)	301-827-5849 , Team Leader

Overall Recommendation:
Establishment:

CO

DMF No:	AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER	
Profile: TCM	OAI Status: NONE
Estab. Comment: MFG, PACKAGED LABELED AND RELEASE AND STABILITY TESTING ON FINISHED DOSAGE FORM (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301- 827-5846)	

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment: 2437838
ENDO PHARMACEUTICALS INC
500 ENDO BLVD
GARDEN CITY, NY 11530

DMF No:	AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER	
Profile: CTL	OAI Status: NONE
Estab. Comment: ALTERNATE TESTING SITE FOR RELEASE AND STABILITY OF THE FINISHED PRODUCT (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)	

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment:

INC

DMF No:	AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER	
Profile: CSN	OAI Status: NONE
Estab. Comment: MFG ADDRESS IN JACKET IS () (HFD-613) 301-827-5846	

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 40341/000
Stamp: 09-NOV-1998
Regulatory Due: . . .
Applicant: ENDO PHARMS
500 ENDO BLVD
GARDEN CITY, NY 11530

Action Goal:
District Goal: 09-OCT-1999
Brand Name:
Estab. Name: OXYCODONE; ACETAMINOPHEN
Generic Name:

Priority:
Org Code: 600

Dosage Form: (TABLET)
Strength: 7.5/500 MG 10/650 MG

Application Comment:

FDA Contacts: T. AMES (HFD-617) 301-827-5849 , Project Manager
U. VENKATARAM (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

Establishment:

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

Estab. Comment: MFG, PACKAGED LABELED AND RELEASE AND STABILITY TESTING ON
FINISHED DOSAGE FORM (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-
827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment: 2437838

ENDO PHARMACEUTICALS INC
500 ENDO BLVD
GARDEN CITY, NY 11530

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: ALTERNATE TESTING SITE FOR RELEASE AND STABILITY OF THE FINISHED
PRODUCT (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment:

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment:
(HFD-613) 301-827-5846 (on 11-DEC-1998 by C. HOLQUIST)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-341

Date of Submission: November 9, 1998

Applicant's Name: Endo Pharmaceuticals, Inc.

Established Name: Oxycodone and Acetaminophen Tablets USP,
7.5 mg/500 mg and 10 mg/650 mg

Proprietary name: Percocet®

Labeling Deficiencies:

1. GENERAL COMMENTS:

We note that the proprietary name, Percocet® you have proposed for these two strengths is identical with the name of your reference listed drug. Your proposed proprietary name "Percocet®" will be forwarded to the CDER Labeling and Nomenclature Committee for review and comment. We believe that this may lead to medication errors particularly if the strength is not specified in an physician's order for Percocet®. You may consider employing a similar numbering system used for "Tylenol with Codeine" to differentiate various strengths of your products. However, we defer final comment on your proposed proprietary name pending notification of the committee's findings.

2. CONTAINER - 100s & 500s

- a. Please note that the presence of FD&C Yellow No. 6 needs to be declared in the labeling, but not on the labels for the prescription drug per 21 CFR 201.20(c). You may delete this statement from the labels if you elect to do so.
- b. Revise to read "Usual Dosage" rather than "dosage".

3. UNIT DOSE BLISTER

Satisfactory in draft

4. BLISTER CARD

See comment under CONTAINER.

5. BLISTER PACK CARTON

a. See comment under CONTAINER.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, include a statement if dispensed to outpatients, it should be with a child resistant container, for example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentence is optional.]

6. INSERT

a. DESCRIPTION

i. Include the pharmacological or therapeutic class for oxycodone hydrochloride. We refer you to 21 CFR 201.57(a) (v).

ii. Revise the third paragraph (Acetaminophen occurs...) as follows:

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a ... taste. It may be represented by the following structural formula [include the structural formula of acetaminophen here].

iii. Include the molecular weight and molecular formula of both acetaminophen and oxycodone. In addition, include the structural formula for acetaminophen. Refer to 21 CFR 201.57(a) (vi) for guidance.

b. CONTRAINDICATIONS

...other components of this... [plural]

c. PRECAUTIONS

i. Drug Interactions

Delete the second paragraph.

ii. Usage in Pregnancy

A) Revise the sub-subsection heading "Pregnancy Category C" to read "Teratogenic Effects; Pregnancy Category C".

B) Nonteratogenic Effects

Use of opioids during... [rather than "narcotics" to be consistent]

d. DOSAGE AND ADMINISTRATION

With respect to the last sentence in this section, include the number of tablets for each strength in parenthesis, which correspond to the maximum allowed daily dose of acetaminophen.

e. HOW SUPPLIED

i. Please delete the statement "NARCAN® is a ...". We refer you to the GENERAL COMMENT under INSERT.

ii. We encourage the inclusion "dispense in..." statement as found on your container labels.

iii. The name and place of the manufacturer appearing in this section is not identical with the one described in your "Description of Manufacturing Facility" statement. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit in draft. We will not request final print pending the findings of the Labeling and Nomenclature committee regarding your proposed proprietary name.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0316
Expiration Date: December 31, 1997
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

APPLICANT Pharmaceuticals Inc.	DATE OF SUBMISSION 8/24/98
PHONE NO. (Include Area Code) (616) 522-3309	FACSIMILE (FAX) Number (Include Area Code) (516) 832-2291
ADDRESS (Number, Street, City, State, County, and ZIP Code or Mail Code) Endo Blvd. Green City, NY 11530	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, State, and ZIP Code telephone & FAX number) IF APPLICABLE

OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE NUMBER (If previously issued)

DESCRIPTION

GENERIC NAME (e.g., Proper name, USP/USAN name) Codeine and Acetaminophen Tablets, USP	PROPRIETARY NAME (trade name) IF ANY Percocet®
CHEMICAL NAME (If any) 14-hydroxydihydrocodeinone and hydroxy-acetanilide	CODE NAME (If any)
FORM Tablets	STRENGTHS: 2.5 mg/325 mg and 5 mg/325 mg
ROUTE OF ADMINISTRATION: Oral	
INDICATIONS FOR USE: the relief of moderate to moderately severe pain.	

APPLICATION INFORMATION

APPLICATION TYPE		
<input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input checked="" type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGIC APPLICATION (21 CFR part 601)		
ANDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507		
OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Holder of Approved Application		
Percocet® Tablets 5 mg/325 mg Endo Pharmaceuticals Inc.		
SUBMISSION		
<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> NOTIFICATION	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT		
REASON FOR SUBMISSION Original Application.		
MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED 4	THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC	

MANUFACTURING INFORMATION

Locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

attached.

RECEIVED

References (list related Licenses Application, NDAs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current

AUG 25 1998

attached.

GENERIC DRUGS

A 3439 (5/96)

II. BASIS FOR ANDA
SUBMISSION

III. PATENT CERTIFICATE/
EXCLUSIVITY STATEMENT

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: ANDA 40341/000
Stamp: 09-NOV-1998
Regulatory Due:
Applicant: ENDO PHARMS
500 ENDO BLVD
GARDEN CITY, NY 11530

Action Goal:
District Goal: 09-OCT-1999
Brand Name:
Estab. Name: OXYCODONE; ACETAMINOPHEN
Generic Name:

Priority:
Org Code: 600

Dosage Form: (TABLET)
Strength: 7.5/500 MG 10/650 MG

Application Comment:

FDA Contacts: T. AMES (HFD-617) 301-827-5849 , Project Manager
U. VENKATARAM (HFD-647) 301-827-5849 , Team Leader

Overall Recommendation:

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCM OAI Status: NONE
Estab. Comment: MFG, PACKAGED LABELED AND RELEASE AND STABILITY TESTING ON
FINISHED DOSAGE FORM (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment: 2437838

ENDO PHARMACEUTICALS INC
500 ENDO BLVD
GARDEN CITY, NY 11530

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: ALTERNATE TESTING SITE FOR RELEASE AND STABILITY OF THE FINISHED
PRODUCT (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment:

5

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: 246 (on 11-DEC-1998 by C. HOLQUIST
(HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN

OAI Status: NONE

Estab. Comment: MFG OXYCODONE HYDROCHLORIDE (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment:

DMF N

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN

OAI Status: NONE

Estab. Comment: MFG ACETAMINOPHEN USP THEN SENT TO GREENVILLE PLANT
TO MANUFACTUR (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

Establishment:

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM

OAI Status: NONE

Estab. Comment: BLISTER PACKAGING OF THE COMMERCIAL BATCHES FOR THIS PRODUCT (on 08-DEC-1998 by C. HOLQUIST (HFD-613) 301-827-5846)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-DEC-1998				HOLQUISTC

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-341

Date of Submission: November 9, 1998

Applicant's Name: Endo Pharmaceuticals, Inc.

Established Name: Oxycodone and Acetaminophen Tablets USP,
7.5 mg/500 mg and 10 mg/650 mg

Proprietary name: Percocet®

Labeling Deficiencies:

1. GENERAL COMMENTS:

We note that the proprietary name, Percocet® you have proposed for these two strengths is identical with the name of your reference listed drug. Your proposed proprietary name "Percocet®" will be forwarded to the CDER Labeling and Nomenclature Committee for review and comment. We believe that this may lead to medication errors particularly if the strength is not specified in an physician's order for Percocet®. You may consider employing a similar numbering system used for "Tylenol with Codeine" to differentiate various strengths of your products. However, we defer final comment on your proposed proprietary name pending notification of the committee's findings.

2. CONTAINER - 100s & 500s

- a. Please note that the presence of FD&C Yellow No.6 needs to be declared in the labeling, but not on the labels for the prescription drug per 21 CFR 201.20(c). You may delete this statement from the labels if you elect to do so.
- b. Revise to read "Usual Dosage" rather than "dosage".

3. UNIT DOSE BLISTER

Satisfactory in draft

4. BLISTER CARD

See comment under CONTAINER.

5. BLISTER PACK CARTON

a. See comment under CONTAINER.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, include a statement if dispensed to outpatients, it should be with a child resistant container, for example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[Note: The second sentence is optional.]

6. INSERT

a. DESCRIPTION

i. Include the pharmacological or therapeutic class for oxycodone hydrochloride. We refer you to 21 CFR 201.57(a)(v).

ii. Revise the third paragraph (Acetaminophen occurs...) as follows:

Acetaminophen; 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a ... taste. It may be represented by the following structural formula [include the structural formula of acetaminophen here].

iii. Include the molecular weight and molecular formula of both acetaminophen and oxycodone. In addition, include the structural formula for acetaminophen. Refer to 21 CFR 201.57(a)(vi) for guidance.

b. CONTRAINDICATIONS

...other components of this... [plural]

c. PRECAUTIONS

i. Drug Interactions

Delete the second paragraph.

ii. Usage in Pregnancy

A) Revise the sub-subsection heading "Pregnancy Category C" to read "Teratogenic Effects; Pregnancy Category C".

B) Nonteratogenic Effects

Use of opioids during... [rather than "narcotics" to be consistent]

d. DOSAGE AND ADMINISTRATION

With respect to the last sentence in this section, include the number of tablets for each strength in parenthesis, which correspond to the maximum allowed daily dose of acetaminophen.

e. HOW SUPPLIED

i. Please delete the statement "NARCAN® is a ...". We refer you to the GENERAL COMMENT under INSERT.

ii. We encourage the inclusion "dispense in..." statement as found on your container labels.

iii. The name and place of the manufacturer appearing in this section is not identical with the one described in your "Description of Manufacturing Facility" statement. Please revise and/or comment.

Please revise your labels and labeling, as instructed above, and submit in draft. We will not request final print pending the findings of the Labeling and Nomenclature committee regarding your proposed proprietary name.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further

review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?			X
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. (new strength)	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			X
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? (see note to chemist)	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C _{max} , T _{max} , T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			X

NOTES/QUESTIONS TO THE CHEMIST:

USP recommends that the product be preserved in tight, light-resistant containers. Is the container proposed light-resistant?

yes
MS 4/23/99

FOR THE RECORD:

1. MODEL LABELING - Percocet® (Oxycodone and Acetaminophen HCL, 5 mg/325 mg, Endo); Approved April 30, 92). This is ANDA 85-106/s-106.

As a reference, the followings are the dates on which other Oxycodone/Acetaminophen containing RLD products' insert labeling last approved.

88-790/S-008 Tylox® Capsules (5 mg/500 mg, Johnson) -
5/30/91

89-775/S-004 Roxicet® Tablets (5 mg/500 mg, Roxane) -
5/7/92

2. These two new strengths were found suitable for ANDA application through the Agency's approval of the firm's Suitability Petition on November 6, 1998.
3. Regarding the GENERAL COMMENT on proprietary name, the following is the e-mail sent to Dan Boring, Chairman of the LNC committee.

Endo Laboratories has filed an ANDA for higher strengths of Percocet (Oxycodone and APAP, 7.5 mg/500 mg & 10 mg/650 mg), whose filing was accepted through citizen's petition. The firm has proposed the proprietary name, Percocet, which is identical with the original percocet tablet (5 mg/325 mg). We believe that this may lead to medication errors particularly if the strength is not specified in a physician's order for Percocet®. I am inclined to suggest that the firm may consider employing a similar numbering system used for "Tylenol with Codeine" to differentiate various strengths of percocet products. I would like to hear your opinion in this matter. Thank you for your help.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 21, 22 & 168 (Volume B.1.1).
5. The firm has replaced the term "narcotics" with "opioids" throughout the text and it should be acceptable.
6. The firm has committed that the firm's various strengths will be differentiated by using different print colors.
7. PATENTS/EXCLUSIVITIES

No issue

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

9. DISPENSING STATEMENT

RLD & ANDA - Dispense in a tight, light-resistant container as defined in the USP.

USP - Preserve in tight, light-resistant containers.

10. USP labeling requirement

The tablets may be labeled to indicate the content of oxycodone hydrochloride equivalent. Each mg of oxycodone is equivalent to 1.116 mg of oxycodone hydrochloride.

11. PACKAGING CONFIGURATIONS

RLD: 100s, 500s, and unit-dose 100s.

ANDA: Same as RLD

12. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. See Vol.B.1.3, P.648.

13. SCORING

The RLD, Percocet® (Oxycodone and Acetaminophen, 5 mg/325 mg) by this firm is bisected whereas these two new strengths (filed by Citizen's Petition) are not scored.

14. Container/CLOSURE

Container: Plastic

Closure: CRC (SafeGard) for 100s & 500s

See comment to the chemist.

15. The firm has included a statement to read "The total daily dose of acetaminophen should not exceed 4 grams." As a last sentence under D&A section. Although this does not appear in the insert labeling of RLD yet, we should allow the firm to retain this statement. Refer to the e-mail between dr. Scheinbaum and Chan Park on this issue. Also refer to the comment under DOSAGE AND ADMINISTRATION in this review. Currently, we are awaiting for the approval of this labeling change of NDA reference listed drug Percodan (Endo, 07-337).

(Question)

Endo Laboratories has filed an ANDA for higher strengths of Percocet (Oxycodone and APAP, 7.5 mg/500 mg & 10 mg/650 mg), whose filing was accepted through citizen's petition. The firm has proposed the proprietary name, Percocet, which is identical with the original percocet tablet (5 mg/325 mg).

We believe that this may lead to medication errors particularly if the strength is not specified in a physician's order for Percocet®. I am inclined to suggest that the firm may consider employing a similar numbering system used for "Tylenol with Codeine" to differentiate various strengths of percocet products. I would like to hear your opinion in this matter. Thank you for your help.

(Answer)

I believe it is important to state the maximum number of pills allowed. Not every doctor will remember the amount of APAP in each pill. Few will bother to look much at the label. Some may have difficulty calculating what 4 g implies and make errors. The easiest thing to remember or look up is the maximum number of pills per day for each strength.

16. We will ask the firm to delete the second paragraph "The use of MAO inhibitors... or oxycodone." appearing in the PRECAUTIONS, Drug Interactions. This statement has been marked off from RLD insert labeling without explanation. Another generic labeling for this product (ANDA 87-406, Barr), approved January 24, 1994 (This is after the last approval of RLD insert labeling), DOES NOT CONTAIN this statement.

Date of Review: 1/25/99

Date of Submission: 11/9/98

Primary Reviewer: Chan Park

Chan Park 2/9/99
Date:

Team Leader:

Date:

cc:

Chan Park 2/10/99

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

40-341

APPLICATION NUMBER:

CORRESPONDENCE



Endo Pharmaceuticals Inc.

July 20, 1999

NEW CORRESP

NC

hard copy

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

**Re: ANDA 40-341; Oxycodone and Acetaminophen Tablets, USP
7.5 mg/500 mg and 10 mg/650 mg
Telephone Amendment - Withdrawal of**

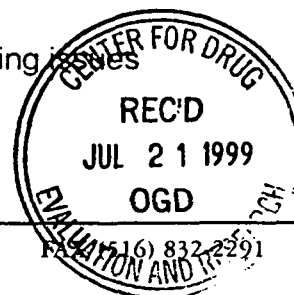
Dear Mr. Sporn:

Reference is made to my conversation today with Mr. Tim Ames, Project Manager, FDA, with regards to one of the outside firms referenced in the subject drug product application.

_____ is referenced in our ANDA as a testing site for microbial testing of _____. Mr. Ames indicated that cGMP certification has expired and the FDA will therefore need to inspect their facility. He also indicated that this inspection will significantly delay the approval of our application, and has therefore requested that Endo withdraw _____ from the application and use another testing facility that is in our application, since all other firms have been found to be satisfactory.

Please note that our manufacturing and testing facility, _____ Company is capable of doing the microbial test for _____ and has been doing this test since April 20, 1998 or earlier. As per the Agency's request, we are therefore amending this application with a request to withdraw _____ and use _____ Company to perform the microbial test. _____ will no longer be used as a testing facility for the subject drug product unless a pre-approval supplement is filed as requested by the FDA.

It is our understanding that this amendment finalizes all outstanding issues with this application.



We now anxiously await the approval of this ANDA. If there are any questions, please contact me at (516) 522-3305.

Sincerely,

A handwritten signature in black ink, appearing to read "Carol Patterson", with a long horizontal flourish extending to the right.

Carol A. Patterson, MS
Manager, Regulatory Affairs

CAP:wj
FDA-1999.doc



Endo Pharmaceuticals Inc.

**CMC/ESD AMENDMENT
FACSIMILE AMENDMENT**

June 30, 1999

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

NC to Fax

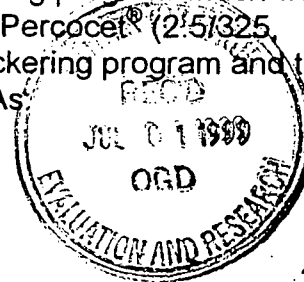
**Re: ANDA 40-341; Oxycodone and Acetaminophen Tablets, USP
7.5 mg/500 mg and 10 mg/650 mg
Labeling Responses to June 3, 1999 Deficiency Letter**

Dear Mr. Sporn:

Reference is made to the attached facsimile letter dated June 3, 1999 which contains both labeling, and CMC (chemistry, manufacturing and controls) comments on the original application submitted November 9, 1999 for the subject product. The response to the CMC comments dated June 16, 1999 has been faxed and mailed to Office of Generic Drugs. The response to the labeling deficiencies is being submitted in this amendment.

Reference is also made to my teleconferences on June 5th and 15th with Mr. Bob West, Division Director, Mr. Charlie Hoppess, Supervisor and Mr. Adolph Vezza, Project Manager, of the Labeling Division with regards to the need for a "Potency Sticker" for all of the new strengths of Percocet[®] (oxycodone and acetaminophen tablets).

The discussions in the teleconferences pertain to FDA's concern for potential medication errors when additional new strengths of Percocet[®] (2.5/325, 7.5/500 and 10/650 mg) are introduced into the market. FDA therefore requested Endo Pharmaceuticals to implement a stickering program which would alert the medical profession to all available strengths of Percocet[®] (2.5/325, 5/325, 7.5/325 and 10/650 mg). Endo agreed to the stickering program and the FDA's wording on the sticker for the following two ANDAs:



- ANDA 40-330
Oxycodone and Acetaminophen Tablets, USP
2.5 mg/325 mg, 5 mg/325 mg which was approved on June 25, 1999
- ANDA 40-341
Oxycodone and Acetaminophen Tablets, USP
7.5 mg/500 mg, 10 mg/650 mg which is the subject of this application

In accordance with an earlier request made by FDA, Endo makes the commitment to submit a Changes Being Effected (CBE) supplement with the production sticker labels with a 30 day waiting time before implementation.

Included in this amendment are the following:

- Completed FDA Form 356h
- A copy of FDA's June 3, 1999 Facsimile Deficiency Letter
- Labeling response and final printed labeling which include the sticker which were agreed to by FDA
 - 12 copies final printed package insert
 - 12 copies of final printed container labels
 - 12 copies of final printed blister labeling
 - 2 diskettes (Archival and Review) which contain the CMC ESD amendment

The following is our understanding of the status of the review of this application:

Pre-Approval Inspection for:

- Manufacturing facility, _____ was
waived in a letter dated December 24, 1998.
- Blister Packaging Facility, _____ New
satisfactory.

Bioequivalence: The attached FDA letter (June 3, 1999), indicates that the review has been completed with no further comments.

Methods Validation: As per Mr. Tim Ames, Project Manager, Office of Generic Drugs, Methods Validation is not necessary since the product is USP.

CMC: The response to the CMC comments in the June 3, 1999 facsimile deficiency letter was submitted June 16, 1999.

Labeling: Comments were received in the June 3, 1999 facsimile deficiency letter and the responses will be submitted under separate cover.

If there are any questions regarding this amendment or any further open issues on this application, please contact me at (516) 522-3305.

Sincerely,

A handwritten signature in black ink, appearing to read 'Carol A. Patterson', with a long horizontal line extending to the right.

Carol A. Patterson, MS
Manager, Regulatory Affairs

attachments

CAP:wj
FDA-1999.doc



Endo Pharmaceuticals Inc.

FACSIMILE AMENDMENT

June 16, 1999

NEW CORRESP

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

**Re: ANDA 40-341; Oxycodone and Acetaminophen Tablets, USP
7.5 mg/500 mg and 10 mg/650 mg
Facsimile Amendment**

Dear Mr. Sporn:

Reference is made to the June 3, 1999 facsimile letter from the Agency containing Chemistry, Manufacturing and Controls and labeling comments on the original application dated November 9, 1998 for the subject product.

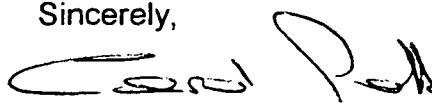
We are amending the application with our responses to your comments. As per my conversation with Mr. Adolph Vezza in the Labeling Division, we will submit a response to the labeling comments and provide final printed labeling under a separate cover. The electronic submission for this paper amendment will also be submitted along with the labeling response.

Included in this amendment are the following:

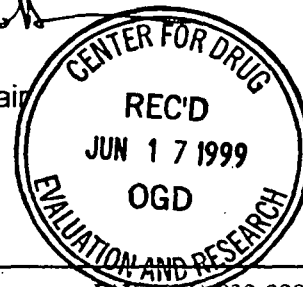
- Completed FDA Form 356h
- Field Copy Certification
- A copy of FDA's June 3, 1999 Facsimile Letter
- CMC Responses

If there are any questions regarding this amendment, please contact me at (516) 522-3305.

Sincerely,


Carol Patterson
Manager, Regulatory Affairs

enclosures



JUN - 3 1999

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-341 APPLICANT: Endo Pharmaceuticals
DRUG PRODUCT: Oxycodone and Acetaminophen Tablets USP
7.5 mg/500 mg, 10 mg/650 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. The amount of Microcrystalline Cellulose shown in your composition statement should not be considered accurate since it will always be reduced by a significant amount when you compensate for the amount of contained in Please revise your composition statements to more accurately reflect the amount of Microcrystalline Cellulose prior to compensating for the assay value of instead of the assay value of Acetaminophen in
2. The Certificates of Analysis submitted for the inactive ingredients indicate the use of FD&C Yellow #6 not D&C Yellow #6 , in the 7.5 mg/500 mg tablet. Please submit revised Components and Composition Statements indicating the use of FD&C Yellow #6
3. Your blend uniformity specification indicated an RSD limit of and indicated that testing would only occur for the first three validation batches. Please revise your specifications to indicate a RSD value of and testing of all commercial batches.
4. Your in-process tablet weight specifications are shown as Please confirm that the individual tablet weight specifications include a range of and indicate if this parameter is monitored by averaging individual tablet weights or weighing several tablets at once to determine the average.

5. As noted in your application, the Oxycodone values appeared to decrease during the accelerated stability testing in the blister packaging. While the values remained within specifications, please submit all room temperature stability data accrued to date to support your proposed expiry dating of 24 months.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We note that you have submitted alternate analytical methods to be used in the testing of drug substance and/or drug product. Please be advised that approval to use an analytical procedure that differs from that in the USP does not release your firm from any obligations to comply with the methods and procedures in the USP. You should be aware that USP procedures remain the regulatory method, and results obtained thereof will rule in the event of a dispute.

Sincerely yours,

A handwritten signature in cursive script that reads "M Smela for". The signature is written in dark ink and is positioned above a horizontal line.

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-341

APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Acetaminophen/Oxycodone Tablets
500 mg/7.5 mg and 650 mg/10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Endo Pharmaceuticals Inc.

7145

NEW CORRRESP

CMC ESD
BA/BE ESD

NC

December 11, 1998

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

N40-341

**Re: ELECTRONIC SUBMISSION (CMC & BA/BE)
Oxycodone and Acetaminophen Tablets, USP
7.5 mg/500 mg and 10 mg/ 650 mg**

Dear Mr. Sporn:

Reference is made to our Original Abbreviated New Drug Application submitted November 9, 1998 for the above-referenced drug product.

We are submitting herein the Electronic Submission Documents (ESD) for the chemistry, manufacturing and controls information and the bioequivalence section of the ANDA in accordance with the 45-day grace period allowed by OGD during the CMC ramp-up implementation period.

Enclosed in this submission are four (4) diskettes containing the CMC and BA/BE Electronic Submissions, each in duplicate. The CMC submission consists of the electronic submission document (ESD), the EVA export log file, and the CMC companion document. The Bioequivalence submission files include the BA/BE ESD, the EVA export log file, and the BA/BE companion document.

Our application for this drug product includes a request for waiver of *in-vivo* bioequivalence studies (biowaiver) for both strengths. We have prepared the applicable portions of the electronic submission for Bioequivalence to reflect the product information and dissolution data supporting the biowaiver, in order to help test the ability of the system to handle this situation (as discussed with Richard Sponaugle during training at the University of Maryland).

RECEIVED

DEC 14 1998

GENERIC DRUGS

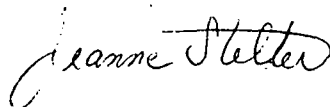
Please note that on August 24, 1998, we submitted an Abbreviated New Drug Application for two other strengths of the same product, Percocet®, based on a separate Suitability Petition. The electronic submission for this ANDA was submitted on October 5, 1998. The application submitted herein and ANDA 40-330 share much common information since the various strengths of the product were developed concurrently and use the same active drug substance supplier, DMF references, manufacturing process, test methodology and specifications.

We hereby declare that, to the best of our knowledge, the information contained in this electronic submission is the same as the November 9, 1998 paper submission. The presentation of the information may differ in order to conform to the ESD/EVA template. For example, for the Manufacturing Process Step form, the manufacturing steps for the blank and executed batch records have been organized into seven major steps, consistent with the Process Flow Diagram (see page 250 of the original ANDA).

Endo Pharmaceuticals Inc. is very pleased to participate in OGD's electronic submissions initiative for the CMC and bioequivalence sections of the ANDA. During the preparation of this electronic submission, , provided consultative assistance. We provided our comments and observations to her, as well as receiving her helpful advice. We would also appreciate your feedback regarding this submission.

If there are any questions or comments, please contact me at (516) 522-3306.

Sincerely,

A handwritten signature in cursive script that reads "Jeanne Stelter".

Jeanne Stelter
Regulatory Associate

enclosures

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-341 APPLICANT: Endo Pharmaceuticals
DRUG PRODUCT: Oxycodone and Acetaminophen Tablets USP
7.5 mg/500 mg, 10 mg/650 mg

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. The amount of Microcrystalline Cellulose shown in your composition statement should not be considered accurate since it will always be reduced by a significant amount when you compensate for the amount of contained in Please revise your composition statements to more accurately reflect the amount of Microcrystalline Cellulose prior to compensating for the assay value of instead of the assay value of in
2. The Certificates of Analysis submitted for the inactive ingredients indicate the use of FD&C Yellow #6 not D&C Yellow #6 ake, in the 7.5 mg/500 mg tablet. Please submit revised Components and Composition Statements indicating the use of FD&C Yellow #6
3. Your blend uniformity specification indicated an RSD limit of and indicated that testing would only occur for the first three validation batches. Please revise your specifications to indicate a RSD value of and testing of all commercial batches.
4. Your in-process tablet weight specifications are shown as Please confirm that the individual tablet weight specifications include a range of and indicate if this parameter is monitored by averaging individual tablet weights or weighing several tablets at once to determine the average.

5. As noted in your application, the Oxycodone values appeared to decrease during the accelerated stability testing in the blister packaging. While the values remained within specifications, please submit all room temperature stability data accrued to date to support your proposed expiry dating of 24 months.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

We note that you have submitted alternate analytical methods to be used in the testing of drug substance and/or drug product. Please be advised that approval to use an analytical procedure that differs from that in the USP does not release your firm from any obligations to comply with the methods and procedures in the USP. You should be aware that USP procedures remain the regulatory method, and results obtained thereof will rule in the event of a dispute.

Sincerely yours,

M Smela for

5/28/99

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-341

APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Acetaminophen/Oxycodone Tablets
500 mg/7.5 mg and 650 mg/10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-341

Endo Pharmaceuticals Inc.
Attention: Andrew G. Clair
500 Endo Blvd.
Garden City, NY 11530

DEC 11 1998

|||||

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Oxycodone and Acetaminophen Tablets USP,
7.5 mg/500 mg and 10 mg/650 mg

DATE OF APPLICATION: November 9, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 9, 1998

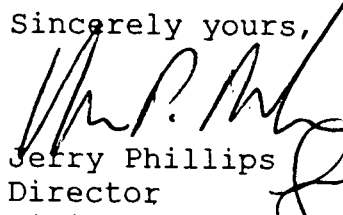
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,


Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



Endo Pharmaceuticals Inc.

**CMC ESD
BA/BE ESD**

(to be filed within 45 days)

November 9, 1998

OK.
C. H. [signature]
11/25/98

Douglas Sporn
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**Re: Original Abbreviated New Drug Application
Oxycodone and Acetaminophen Tablets, USP
7.5 mg/500 mg and 10 mg/650 mg**

Dear Mr. Sporn:

Pursuant to 21 CFR 314.94 and Section 505(j) of the Federal Food, Drug and Cosmetic Act, Endo Pharmaceuticals Inc. ("Endo") hereby submits this original Abbreviated New Drug Application for the above referenced new strengths of Oxycodone and Acetaminophen Tablets, 7.5 mg/ 500 mg and 10 mg/650 mg, both of which will be branded as Percocet® 7.5 mg/500 mg and Percocet® 10 mg/650 mg respectively. The reference listed drug product is Endo's current Percocet® Tablets, 5 mg/325 mg, (ANDA 85-106).

The new strengths of Oxycodone and Acetaminophen Tablets proposed in this ANDA (7.5 mg/500 mg and 10 mg/650 mg) were found suitable for submission as an ANDA via approval of our Suitability Petition (Petition Doc. No. 98P-0105/CP1). A copy of the suitability petition approval letter is enclosed in Section II – "Basis for ANDA Submission".

Please note that on August 24, 1998, we submitted an Abbreviated New Drug Application for two other strengths of the same product, Percocet®. ANDA 40-330 included a new strength, 2.5 mg/325 mg and a reformulation of the currently approved 5 mg/325 mg strength.

The application submitted herein and ANDA 40-330 share many common documents since the various strengths of the product were developed concurrently and use the same active drug substance supplier, DMF references, manufacturing process, test methodology and specifications.

We are requesting a waiver of the requirement to perform in-vivo bioequivalence studies based on the "AA" rating of the reference-listed drug, Percocet® Tablet, 5 mg/325 mg. To support this waiver, we have enclosed in Volume 1.5, analytical test results for the proposed new strengths and comparative analytical and dissolution data between these and the reference listed drug, in conformance with OGD requirements.

This ANDA consists of five volumes submitted in duplicate as archival and technical review copies. The archival copy of the application consists of five volumes in blue jackets designated as Volumes 1.1 to 1.5. The technical review copy of this application consists of Volumes 1.1 to 1.4 in red jackets (Chemistry, Manufacturing and Controls information and Labeling) and Volume 1.5 (Bioequivalence Waiver and associated documentation) in an orange jacket. In addition, the Methods Validation Package (Section XVI) has been submitted, in duplicate, in separate black binders.

The following information is provided for clarification during the review:

- Name of Drug Product
Several names are included in the submitted documentation that were used interchangeably during the development of the two strengths that are the subject of this ANDA. These names are synonymous and they are: EN3200, Percocet® Variant, Percocet®, and Oxycodone and Acetaminophen Tablets.
- Company Name Changes
Endo Pharmaceuticals Inc. is an independent, fully integrated pharmaceutical company that was formed as a result of a management buy-out from The DuPont Merck Pharmaceutical Company. The Management buy-out which concluded in August 1997 included the acquisition by Endo Pharmaceuticals Inc. of DuPont Merck's wholly owned generic subsidiary, Endo® Laboratories, L.L.C. and several other products and assets.

On July 1, 1998, the joint venture between DuPont and Merck which created The DuPont Merck Pharmaceutical Company came to an end with the formal dissolution of the joint venture entity. As such, the old DuPont Merck entity is now incorporated into the DuPont Pharmaceuticals Company, part of DuPont Life Sciences Enterprise.

Since the name change from DuPont Merck to DuPont Pharmaceuticals Company occurred recently, much of the documentation in this ANDA reflects the DuPont Merck name.

- Samples

Please send the request for samples for Methods Verification Studies to the attention of:

Andrew G. Clair, Ph.D.
Endo Pharmaceuticals Inc.
500 Endo Blvd.
Garden City, NY 11530

Notification of Electronic Submission

An electronic submission of the information contained in this ANDA will be filed within 45 days of the filing of the paper ANDA in accordance with the guidelines issued by the Office of Generic Drugs. Endo Pharmaceuticals Inc. hereby declares that to the best of our knowledge, the data contained in the electronic submission will be the same as in this paper submission unless otherwise noted.

Endo Pharmaceuticals Inc. certifies that a copy of the chemistry, manufacturing and controls section of the ANDA (Volume 1.1 to 1.4) and field copy certification have concurrently been sent to the New York District Office.

Please be advised that the materials and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the application provision 18 U.S.C. Section 331(j).

Any questions regarding this application may be directed to me at (516) 522-3305. Any written communications may be faxed to me at (516) 832-2291.

Sincerely,



Carol Patterson, M.S.
Manager, Regulatory Affairs

attachments

CAP:wj
FDA-1998(cont'd)